Clinical significance of inflammatory markers in polycystic ovary syndrome: Their relationship to insulin resistance and Body Mass Index

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Abstract. *Background*: Women with polycystic ovary syndrome (PCOS) have an increased prevalence of insulin resistance (IR) and related disorders. Elevated serum levels of high sensitivity CRP (hs-CRP), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) reflect low-grade chronic inflammation and have been associated with several insulin-resistant states; they are useful cardiovascular risk markers. The objective of this study was to investigate whether soluble inflammatory markers are altered in PCOS focusing on its relationship with obesity and indexes of insulin resistance.

Patients and methods: One hundred and eight women with PCOS and 75 healthy women were recruited. Patients were divided according to body mass index (BMI) into two groups; group I (BMI < 27 kg/m^2) and group II (BMI $\geqslant$ 27 Kg/m^2). Serum levels of hs-CRP, IL-6, and TNF-α, lipid and hormone profiles were measured.

Results: PCOS patients had increased levels of testosterone, luteinizing hormone (LH), androstendione, insulin level and HOMA index compared to healthy BMI matched controls. High-density lipoprotein (HDL) concentrations were significantly reduced in both patient groups compared to their controls, while triglyceride levels were significantly increased in obese group compared to controls. There were no significant difference in serum inflammatory markers hs-CRP, IL-6 and TNF-α between group I and their matched controls. On the other hand, there were significant increase in these markers between group II and their matched controls. There were highly significant positive correlation between hs-CRP and IL-6 ($r = 0.702$, $P < 0.001$) and between hs-CRP and TNF-α ($r = 0.621$, $P < 0.001$), also between IL-6 and TNF-α ($r = 0.543$, $P < 0.001$). These inflammatory markers correlated significantly with BMI and HOMA index. Multiple regression analysis revealed that BMI and HOMA were predictors of IL-6 levels ($b = 11.173$, $P < 0.001$, $b = 13.564$, $P < 0.001$ respectively) and BMI was the only predictor of hs-CRP levels ($b = 12.578$, $P < 0.001$) and TNF-α levels ($b = 0.134$, $P < 0.001$).

Conclusion: PCOS and obesity induce an increase in serum inflammatory cardiovascular risk markers. The precise mechanisms underlying these associations require additional studies to clarify the state of the cardiovascular system in women with PCOS compared with controls in large numbers of patients to determine the relative contribution of different factors including insulin resistance, androgen status and BMI.

Keywords: Polycystic ovary syndrome, inflammatory markers, insulin resistance, BMI

1. Introduction

The polycystic ovary syndrome (PCOS) is one of the most common reproductive abnormalities, affecting 5–10% of the population in the reproductive age [1]. Polycystic ovary syndrome (PCOS) encompasses different levels of manifestation. Clinical features include anovulation, hirsutism and obesity, whereas bio-

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logical changes are reflected through elevated LH, impaired LH/FSH relation and elevated testosterone levels. Hyperandrogenism is partly linked to hyperinsulinism caused by insulin resistance. Morphological signs are manifested as atypical ultrasonographic appearance of polycystic ovaries [2]. In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) revised the definition of PCOS [3]; the syndrome is now defined as the presence of any two of the following three criteria: polycystic ovaries, oligo/anovulation and/or clinical or biochemical evidence of hyperandrogenism.

Numbers of investigations have addressed the possibility that PCOS may also be associated with incremental biochemical and physiological markers of cardiovascular risk, including endothelial dysfunction. Women with PCOS have clustering of cardiovascular risk factors, such as obesity, lipid abnormalities, impaired glucose tolerance and hypertension [4]. They are at high risk of developing coronary heart disease (CHD), as more adverse CHD risk profiles have been demonstrated in women with PCOS [5]. Also, studies have demonstrated a high risk for impaired glucose tolerance and type 2 diabetes mellitus in PCOS [6]. It has not yet been clarified whether this increase in risk is related to endocrine abnormalities associated with PCOS per se, such as hyperandrogenemia, or whether it is a consequence of the anthropometric or metabolic abnormalities frequently observed in PCOS women [7].

During the past years, serum markers of inflammation are being increasingly recognized as predictors of cardiovascular disease [8]. The increased concentration of these inflammatory markers clusters with other cardiovascular risk factors, such as dyslipidemia, glucose intolerance and type 2 diabetes, hypertension, hypofibrinolysis and obesity. Chronic low-grade inflammation has been proposed to play a role in the pathogenesis of insulin resistance and the metabolic syndrome [9]. It has been reported that Proinflammatory genotypes may influence hyperandrogenism and PCOS; it was found that common polymorphisms in the genes encoding TNF, type 2 TNF receptor, IL-6, and the IL-6 signaling molecule gp130 are associated with hyperandrogenism and PCOS, or influence hyperandrogenic phenotypic traits [10,11]. Consistently increased hs-CRP levels have been reported in PCOS patients supporting the hypothesis that PCOS increases cardiovascular and diabetes risk by activating chronic inflammation [12], although other authors showed that inflammatory markers in PCOS patients were not increased when compared with age and BMI matched controls [13,14].

Correlation of circulating inflammatory markers with obesity and insulin resistance are common findings in PCOS [15]. IL-6 expression in adipose tissue correlates with obesity [16]. It is still not known whether these parameters of chronic inflammation are primary or secondary to obesity and/or insulin resistance especially since short term administration of IL-6 in humans failed to impair insulin sensitivity [17].

The adipose tissue plays a central role in the relationship between cytokines and insulin resistance. The expression of TNF-α and TNFR2 in adipose tissue is increased in obesity [18]. TNF-α expression correlates with indexes of insulin resistance and decreases with weight loss in parallel with the improvement in insulin sensitivity [19], similar results have been reported for IL-6 [20]. Moreover, inflammatory cytokines might induce insulin resistance by direct actions on insulin-signaling postreceptor molecules [21] or by inducing central obesity through activation of the hypothalamic-pituitary-adrenal axis [22]. As obesity induces insulin resistance, and inflammatory cytokines are secreted by adipose tissue, it is difficult to evaluate if the relationship between serum markers of inflammation and insulin resistance results from a pathophysiological link, or is merely reflecting the stronger relationship between obesity and insulin resistance [18].

The aim of the present study was to evaluate the circulating concentrations of hs-CRP, IL-6 and TNF-α as serum markers of inflammation in a group of premenopausal women with PCOS compared with healthy controls, focusing on their relationship to insulin resistance and obesity.

2. Patients and methods

One hundred and eight women with PCOS participated in this study. The medical ethical committee of University approved the study and written informed consent was obtained from patients. They were divided according to BMI into two groups; group I (BMI < 27 kg/m^2, age 28.7 ± 5.2 years), group II (BMI $\geqslant 27$ Kg/m^2, age 28.3 ± 4.2 years). All women were euthyroid and not taking any medication or hormones for six months (including oral contraceptive agents) known to affect sex hormones or carbohydrate metabolism. All women were examined clinically (general, gynecologic examination, weight, height) and examined by transvaginal ultrasonography. Patients with overt di-

abetes mellitus and impaired glucose tolerance were excluded from the study.

The diagnosis of PCOS was made on the basis of the revised 2003 Rotterdam ESHRE/ASRM diagnostic criteria [3], women with PCOS meet two of the following three criteria after exclusion of other etiologies (pituitary insufficiency, persistent hyperprolactinemia, congenital adrenal hyperplasia): (1) oligomenorrhea or anovulation; (2) clinical and/or biochemical signs of hyperandrogenism; (3) polycystic ovaries.

Seventy five healthy fertile women matched for BMI and age (27.9 ± 3.5years) without clinical evidence of PCOS with regular menses and ultrasonographically normal ovaries served as control group, their clinical, biochemical and hormonal profiles were within normal limits.

Body mass index (BMI) was calculated for all groups as body weight (kg) divided by body height squared (m^2). Waist/Hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Insulin resistance was assessed by means of the homeostasis model assessment (HOMA), which was measured by multiplying fasting serum insulin (microunits per milliliter) and fasting plasma glucose (micromoles per liter) divided by 22.5 [23].

2.1. Methods

Samples were obtained between days 5 and 10 of menstrual cycle or during amenorrhea after excluding pregnancy. Samples were collected after 12 hours overnight fasting. A 75-g oral glucose tolerance test was performed, samples were obtained for measurement of serum insulin and plasma glucose at 0, 30, 60, 90, and 120 min. Samples were immediately centrifuged, serum were separated and stored at $-70°C$ until analysis.

The samples were analyzed for:

1. Plasma glucose level was estimated by God-PAP enzymatic colorimetric method [24] using Biomerieux test kit, Cat. No. 5 127.
2. Serum insulin was detected by commercially available radio-immunoassay (Abbott IMx Insulin assay) which is a micro-particle Enzyme Immunoassay {MEIA} for the quantitative measurement of human insulin [25].
3. Determination of serum interleukin 6 (IL-6) by solid phase enzyme amplified sensitivity immunoassay (EASIA) performed on micro titer plate using kit supplied by BioSource Europe S.A., Rue de industries, 8 B-1400 Nivelles Belgium [26].

4. Determination of serum high sensitivity C-reactive protein (hs-CRP) by high sensitive immunoassay for measuring human CRP which is a two step sandwich ELISA technique using kit supplied by Diagnostic systems laboratories (DSL-10-42100) Webster, Texas, USA [27].
5. Determination of serum tumor necrosis factor α (TNF-α) by photometric enzyme-linked immunosorbent assay (ELISA) using sterptavidin-coated microtiter plates by kits supplied by Roche Diagnostics GmbH, Roche Molecular Biochemicals, Sandhofer Strasse116 D-68305 Mannheim, Germany [28].
6. Measurement of lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides) by commercial enzymatic methods (Aeroset automated analyzer, Abbott Laboratories, Abbott IL). LDL cholesterol was calculated by using Friedewald's formula [29].
7. Measurement of serum concentration of testosterone, LH and andrestendione by chemiluminescent enzyme immunoassay (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA).

2.2. Statistical analysis

Statistical analyses were performed with STATISTICA software. All text and table values are expressed as means $\pm$ S.D. P values less than 0.05 were considered to be statistically significant. For analysis of parameters, analysis of variance (ANOVA) was used to address differences between PCOS and controls. Bonferroni correction were used for the multiple comparisons when we tested four serum markers in the same set of patients; according to this analysis p values less than 0.0125 were considered to be statistically significant. The nonparametric student-Newman-Keuls multiple comparison test was used to analyze differences between the study groups and controls. Pearson's correlation coefficients were used to test the correlation between variables. Multiple Regression analysis was performed in PCOS patient group for each inflammatory index separately considered as dependent variable and as independent variables; BMI, HOMA, testosterone and androstenedione.

3. Results

The Anthropometric characteristics, hormonal and metabolic profile of PCOS patients and the controls

Table 1
Anthropometric, biochemical and hormonal characteristics of the PCOS and control groups classified according BMI

Parameters	(Normal body weight group) BMI < 27 kg/m^2		(Obese group) BMI $\geqslant 27$kg/m^2		Overall ANOVA test (F)
	Controls	PCOS(GI)	Controls	PCOS(GII)	P value
Numbers	35	56	40	52	
Age(yrs)	26.9 ± 5.4	28.7 ± 5.2	27.5 ± 5.1	28.3 ± 4.2	0.3318 (NS)
BMI(kg/m^2)	22.5 ± 0.5	22.7 ± 0.6	$31.4 \pm 1.2^*$	$32.2 \pm 1.1^{a,*}$	< 0.0001
WHR	0.76 ± 0.01	0.77 ± 0.02	$0.82 \pm 0.02^*$	$0.84 \pm 0.03^{a,*}$	< 0.0001
Fasting insulin (uU/ml)	14.16 ± 1.79	$18.13 \pm 2.45^*$	14.36 ± 2.11	$22.5 \pm 3.9^{a,\dagger,*}$	< 0.0003
Fasting glucose(mg/dl)	83.1 ± 1.56	$86.2 \pm 1.25^*$	85.3 ± 2.4	$89.4 \pm 9.3^{a,\dagger,*}$	< 0.0001
HOMA	1.23 ± 0.5	$2.82 \pm 0.8^*$	1.34 ± 0.17	$4.08 \pm 0.3^{a,\dagger,*}$	< 0.0001
Cholesterol(mg/dl)	160.4 ± 41.3	165.2 ± 38.4	163.2 ± 23.5	$173 \pm 43.5^*$	0.4290 (NS)
LDL(mg/dl)	95.6 ± 23.5	101.8 ± 22.4	97 ± 14.6	$110.4 \pm 32.1^*$	0.0191
HDL(mg/dl)	54.2 ± 15.6	$45.6 \pm 12.7^*$	55.2 ± 14.3	$46.7 \pm 13.4^{*,\dagger}$	0.0008
Triglyceride(mg/dl)	87.5 ± 24.7	92.2 ± 24.2	88.6 ± 35.8	$123.2 \pm 22.6^{a,\dagger,*}$	< 0.0001
Testosterone(ng/ml)	0.58 ± 0.14	$1.05 \pm 0.27^*$	0.62 ± 0.12	$1.32 \pm 0.37^{\dagger}$	< 0.0001
LH (mIU/L)	4.22 ± 2.3	$8.76 \pm 2.6^*$	4.67 ± 2.8	$11.57 \pm 2.5^{a,\dagger,*}$	< 0.0001
Androstenedione (ng/ml)	2.6 ± 0.9	$4.3 \pm 1.6^*$	2.4 ± 0.7	$4.8 \pm 1.3^{*,\dagger}$	< 0.0001

Values are expressed as mean $\pm$ SD.
NS ($P > 0.05$) not significant for overall F test.
$P < 0.05$; $P < 0.01$; $P < 0.001$; $P < 0.0001$ significant for overall F test.
*Significant $p < 0.05$ compared to control (BMI < 27 kg/m^2) $\dagger$ Significant $p < 0.05$ compared to control (BMI $\geqslant 27$kg/m^2).
^{a}Significant $p < 0.05$ compared to PCOS group (BMI < 27 kg/m^2).

Table 2
Inflammatory markers in PCOS and control groups classified according BMI

Parameters	BMI < 27 kg/m^2		BMI $\geqslant 27$kg/m^2		Overall F
	Controls	PCOS(GI)	Controls	PCOS(GII)	test (P)
Numbers	35	56	40	52	
hs.CRP(mg/l)	1.04 ± 0.25	1.67 ± 0.23	1.15 ± 0.22	$3.45 \pm 0.35^{a,\dagger,*}$	< 0.0001
IL-6(pg/ml)	1.25 ± 0.31	1.52 ± 0.34	1.34 ± 0.35	$6.45 \pm 2.27^{a,\dagger,*}$	< 0.0001
TNF-α(pg/ml)	3.66 ± 1.02	3.72 ± 1.26	3.76 ± 1.04	$6.87 \pm 1.12^{a,\dagger,*}$	< 0.001

Values are expressed as mean $\pm$ SD $P < 0.001$; $P < 0.0001$ significant for overall F test.
*Significant $p < 0.05$ compared to control (BMI < 27 kg/m^2) $\dagger$ Significant $p < 0.05$ compared to control (BMI $\geqslant 27$kg/m^2).
^{a}Significant $p < 0.05$ compared to PCOS group (BMI < 27 kg/m^2).

are listed in Table 1. As anticipated in PCOS; testosterone, LH and androstendione levels were significantly increased. Furthermore, ANOVAs for markers revealed increase in concentrations of insulin, glucose, HOMA index, triglyceride, LDL &HDL ($p < 0.0003$, $p < 0.0001$, $p < 0.0001$, $p < 0 0.0001$, $p < 0.0191$, & $p < 0.0008$ respectively) between PCOS patients and controls after BMI was controlled by entering it as a covariate (ANCOVAs), also there were no significant differences in serum concentrations of cholesterol and ages in groups. PCOS patients were classified into two groups according to BMI; those with BMI < 27 kg/m^2 (group I) and patients group $\geqslant 27$ kg/m^2 (group II). Both groups had significant increase in surrogate markers of insulin resistance ($P < 0.001$) and significant decrease in HDL concentration ($P < 0.05$) compared to BMI matched controls. Upon comparing both groups of patients; BMI, WHR, insulin, HOMA were significantly increased in obese group.

ANOVAs for inflammatory markers revealed that, PCOS patients presented with significantly increased levels of inflammatory markers compared to controls, even when BMI was controlled for by entering it as a covariate (ANCOVAs), the group effects for hs-CRP, IL-6 and TNF-α were significant ($p < 0.0001$, $p < 0.0001$, $p < 0.001$ respectively) (Table 2).

Upon comparing each group of PCOS with its BMI matched control group there were no significant difference in serum inflammatory markers hs-CRP, IL-6 and TNF-α between group I and its BMI matched controls, while there were significant increase in serum inflammatory markers hs-CRP, IL-6 and TNF-α in group II compared to its BMI matched controls and group I patients (Table 2) and (Figs 1, 2 and 3).
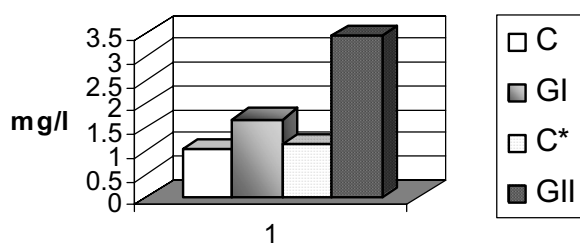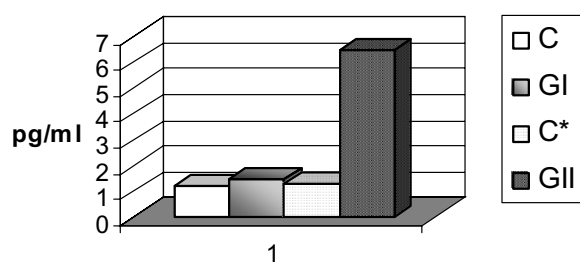
Fig. 1. hs-CRP in different studied groups.

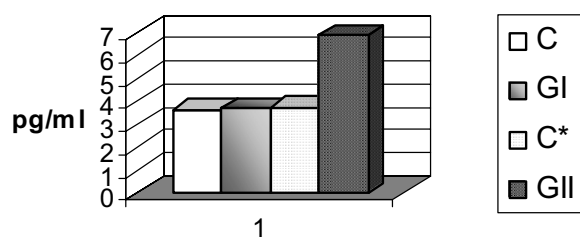Fig. 2. IL-6 in different studied groups.

Fig. 3. TNF-alpha in different studied groups.

Table 3
Correlations of hs-CRP, with other inflammatory markers and biochemical parameters (r value) in all PCOS patients

	hs-CRP	IL-6	TNF-α
hs-CRP	–	0.702**	0.621**
IL-6	0.702**	–	0.543**
TNF-α	0.621**	0.543**	–
BMI(kg/m^2)	0.405*	0.645**	0.503**
HOMA	0.533**	0.522**	0.482*
Cholesterol(mg/dl)	0.165	0.156	0.225
Triglyceride(mg/dl)	0.261	0.232	0.267
HDL(mg/dl)	−0.227	−0.205	−0.146
LDL(mg/dl)	0.177	0.089	0.257
Testosterone(ng/ml)	0.035	0.154	0.067
LH (mIU/L)	0.211	0.189	0.232
Androstenedione (ng/ml)	0.042	0.231	0.038

*Significant $p < 0.05$, **highly significant $p < 0.001$.

in PCOS. BMI and HOMA were predictors of IL-6 levels ($b = 11.173$, $P < 0.001$, $b = 13.564$, $P < 0.001$ respectively), BMI was the only predictor of hs-CRP levels ($b = 12.578$, $P < 0.001$) and TNF-α levels ($b = 0.134$, $P < 0.001$).

4. Discussion

Polycystic ovary syndrome is one of the most common endocrine disorders in humans. In fact, most women with PCOS exhibit features of metabolic syndrome. Thirty year follow-up of 786 women with PCOS revealed significant increase in incidence of diabetes, hypertension and hyperlipidemia compared to the general population [30]. While the association with type 2 diabetes is well established, whether the incidence of cardiovascular disease is increased in women with PCOS remains unclear [31]. Although, studies revealed that women with PCOS have increased prevalence of cardiovascular diseases and higher cardiovascular morbidity even in young and thin women with PCOS [32].

Insulin resistant is no doubt a key component of PCOS. Insulin resistance is involved in the pathogenesis of several disorders, such as type 2 diabetes, central obesity, arterial hypertension and atherosclerosis, finally resulting in cardiovascular disease. These disorders are frequently termed the metabolic syndrome [31]. PCOS has in common with the insulin resistance syndrome increased lipolysis (with a consequent increase in free fatty acid levels) and lipotoxicity of the lean tissues, which would trigger off the development of insulin resistance. There is an abnormal post-receptor sensitivity to catecholamines caused by a defect in the protein kinase A (PKA)-hormonesensitive lipase complex, which would give rise to an increase in lipolysis

Correlation analyses for serum level of inflammatory markers with the studied parameters for the whole population of PCOS are listed in Table 3. There were highly significant positive correlation between hs-CRP and IL-6 ($r = 0.702$, $P < 0.001$) and TNF-α ($r = 0.621$, $P < 0.001$), also between IL-6 and TNF-α ($r = 0.543$, $P < 0.001$) suggesting close link between these markers. Serum hs-CRP, IL-6 and TNF-α correlated significantly with parameter of obesity (BMI) and insulin resistance (HOMA). However, there was, no correlation between inflammatory markers (hs-CRP, IL-6 and TNF-α) and parameters of PCOS such as testosterone, LH and androstendione. Correlation analysis for serum level of inflammatory markers with the studied parameters for the control group revealed significant correlation between hs-CRP and BMI only ($r = 0.465$, $P < 0.001$).

Multiple regression analysis was calculated in order to investigate whether obesity, insulin resistance and/or hyperandrogenism determine markers of inflammation

and free fatty acid levels. These mechanisms might explain the increase in obesity, especially of the visceral type, in women with PCOS [33]. Studies using freshly isolated subcutaneous abdominal adipocytes from women with PCOS have demonstrated obesity-independent post – insulin receptor (IR) – binding resistance to the effects of insulin on glucose transport. In addition, insulin inhibition of lipolysis is impaired in these cells but not in adipocytes isolated from the visceral depot. Studies of skeletal muscle in PCOS have provided evidence for the interaction of intrinsic defects in insulin signaling with factors in the in vivo environment, in the pathogenesis of insulin resistance in this tissue [34].

Chronic inflammation could be involved in the development of metabolic syndrome and cardiovascular disease. Serum markers of chronic inflammation together with insulin resistance are increasingly being considered as cardiovascular risk factors. Atherogenesis is associated with chronic local inflammation, and the inflammatory process could result in the release of cytokines into the circulation such as TNF-α or IL-6 [35]. Moreover, the low-grade chronic inflammatory process associated with atherogenesis might be related to relatively small increases in CRP, only measurable using high sensitivity methods. Increased hs-CRP concentrations are characteristic of obesity, suggesting the existence of low-grade chronic inflammation in this condition [36,37].

In our study, we reported that, both groups of PCOS, obese and non-obese had significant increase of surrogate markers of insulin resistance, these results were in agreement with prior study [38] who stated that the majority of women with PCOS are insulin resistant independent of body weight and that insulin resistance secondary to genetic and lifestyle factors is integral in the pathogenesis, metabolic, clinical features and the long term sequelae in the majority of PCOS patients. However, data on IR in PCOS is inconsistent and influenced by multiple factors, IR methodology varies with fasting insulin, calculated methods and infusion clamps utilized in PCOS research. Fasting insulin and calculated IR based on fasting levels might be inaccurate in PCOS and gold standard clamp methods are not feasible in larger studies or clinical practice, hence there is no ideal measurement [39]. Previous studies documented abnormalities of insulin metabolism in both lean and overweight women with PCOS, and that therapeutic strategies targeting IR in PCOS ameliorate clinical features and might reduce long-term sequelae including diabetes and cardiovascular diseases. The

mainstay for improving IR is lifestyle change; however, feasibility and sustainability remain concerns. In PCOS, metformin reduces IR, improves ovarian function, regulates cycles, lowers androgens, improves clinical hyperandrogenism and potentially improves fertility [40,41]. In a study they demonstrated that overweight/obese women with PCOS have both fasting insulin levels and a HOMA model of insulin resistance almost three times that of controls. Importantly, these findings occurred despite equivalent BMI and WHR and suggest that PCOS per se and not simply body weight is responsible for these differences [42].

In the present study inflammatory markers hr-CRP, IL-6 and TNF-α were significantly increased only in the obese group of patients (BMI $\geqslant 27\text{kg/m}^2$) when compared with the BMI matched controls and the nonobese group. There were significant positive correlation between these inflammatory markers and BMI, HOMA index and each other in the whole patient group. Multiple regression analysis revealed that BMI and HOMA were predictors of IL-6 levels, while BMI was the only predictor of hs-CRP and TNF-α levels. In agreement with our results, previous study demonstrated that the increase in low grade chronic inflammation and in insulin resistance in women with PCOS is associated with central fat excess. Independently of each other, both total body fat as well as central fat excess has a major impact on serum levels of inflammatory mediators, on the WBC, and on estimates of insulin resistance [43]. Previous studies found that, both obesity and central fat excess are closely linked to low-grade chronic inflammation [44,45]. In adipose tissues, many proinflammatory markers (IL-1, IL-6 and TNF-α) as well as anti-inflammatory markers (IL-1Ra) are secreted. CRP is produced in the liver, primarily upon IL-6 stimulation, which is one of the most studied cytokines with proinflammatory and proatherogenic activity [46].

Serum levels of inflammatory markers such as TNF-α, IL-6, and hs-CRP have been found to be elevated in patients with PCOS compared with age and BMI-matched controls. In addition, in young women with PCOS, changes in serum concentrations of IL-6 paralleled the changes of both total and abdominal fat mass [47]. Accordingly, common polymorphisms in the genes encoding TNF-α, soluble type 2 TNF receptor, IL-6, and the IL-6 signaling molecule gp130 were associated with PCOS [48]. Certain adipokines, including TNF-α and others (IL-6, plasminogen activator inhibitor type 1 and adiponectin) associated with increased overall fat, may influence the vascular endothelium in PCOS in a manner independent of elevated CRP and inflammatory changes [49].

In contrast, two studies found that the increase in the inflammatory markers TNF-α, IL-6, and hs-CRP in PCOS was solely caused by obesity, i.e. that PCOS status per se had no effect in these patients and that low grade chronic inflammation may be associated with increased central fat excess [13,14]. Previous study stated that neither hs-CRP nor IL-6 were significantly elevated in lean or obese PCOS compared with age-matched lean or obese controls but they found in agreement with our results that hs-CRP and IL-6 correlated with BMI and insulin resistance but not with parameters of hyperandrogenism [50]. In another study [13], they found that serum markers of inflammation correlated with BMI and insulin resistance in case of PCOS, they stated that decreased insulin sensitivity is known to counteract the physiologic effect of insulin on hepatic acute-phase protein synthesis. Therefore, hepatic IR could lead to increased synthesis of acute-phase proteins, such as CRP. Another possible mechanism is that, cytokines, mainly IL-1, IL-6, and TNFα, may exert stimulating effect on hepatic synthesis of acute-phase proteins [51].

5. Conclusion

PCOS and obesity induce an increase in serum inflammatory cardiovascular risk markers levels. The precise mechanisms underlying these associations require additional studies to clarify the state of the cardiovascular system in women with PCOS compared with controls in large numbers of patients to determine the relative contribution of different factors including insulin resistance, androgen status and BMI.

Conflict of interest

The authors declare that they have no conflict of interest.

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